REMARKS

Entry of the foregoing amendments and favorable consideration of the subject application is respectfully requested in view of the following comments.

Claims 4, 30 and 32 have been amended and claim 33 has been cancelled and new claims 29-33 have been added. Accordingly, claims 4 and 29-32 are presented herein.

Claims 4 and 32 have been amended to delete the term "general" in response to the Examiner's observation that the formula presented is actually a specific, single compound.

Claim 32 has additionally been amended in response to the rejection under 35 U.S.C. §112, to present the claimed product in the form of the preferred amounts of each component and to delete the method step "administered".

Similarly, Claim 30 has been amended to delete the method step "administered as" and to recite the claimed agent in the specifically listed forms.

Claim 33 has been cancelled in that it is more properly drawn to the nonelected method of administering the claimed agent.

Applicants respectfully submit that the foregoing amendments are fully supported by the application as originally filed and neither add new matter nor expand the scope of the claims presented herein and that these amendments may be entered at this time.

Applicants respectfully submit that the foregoing amendments place the application in condition for allowance.

Rejection of Claims Under 35 U.S.C. §112 Second Paragraph

The Office Action rejects claims 30, 32 and 33 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states:

> "Claims 30, 32, and 33 are all drawn to a product, a 'serum cholesterol lowering or preventive or therapeutic agent.' But include the method step 'administered.' Thus, it is unclear whether the claims are intended to be drawn to a product or a method of using the product."

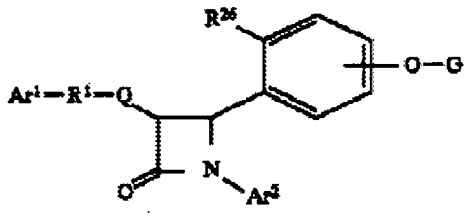
Applicants respectfully submit that the foregoing amendments to claims 30 and 32 and the cancellation of claim 33 have overcome the grounds of rejection under 35 U.S.C. §112, second paragraph or have rendered them moot and respectfully request withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. §103(a)

The Office Action rejects claims 4 and 29-33 under 35 U.S.C. § 103(a) as being unpatentable over Yumibe et al. (U.S. 5,756,470, May 26, 1998, of record) and Tomiyama et al. (U.S. 2004/0063929, April 1, 2004, PTO-1449 submitted April 25, 2006,

English equivalent of WO02/066464, published August 29, 2002, of record). The Office Action states:

> "Yumibe et al teaches a combination of a cholesterol biosynthesis inhibitor and a β-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis [see abstract]. Suitable HMG CoA reductase inhibitors include lovastatin, pravastatin, fluvastatin and simvastatin [column 10, lines 24-27 and claim 17]. The genus of compounds taught by Yumibe et al. is as follows [column 2]:

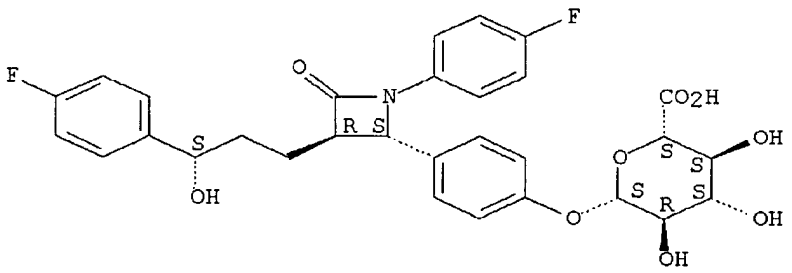


> Wherein R^{26} is H or O-sugar, G is a sugar, and Ar^1 and Ar^2 are aryl or substituted aryl. Specific embodiments are claimed in claim 13 and include the following:

L2 ANSWER 26 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 190448-57-8 REGISTRY
ED Entered STN: 27 Jun 1997
CN β-D-Glucopyranosiduronic acid, 4-[(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl (CA INDEX NAME)

OTHER NAMES:
CN Sch 58235 glucuronide
CN Sch 60663
FS STEREOSEARCH
MF C30 H29 F2 N O9
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



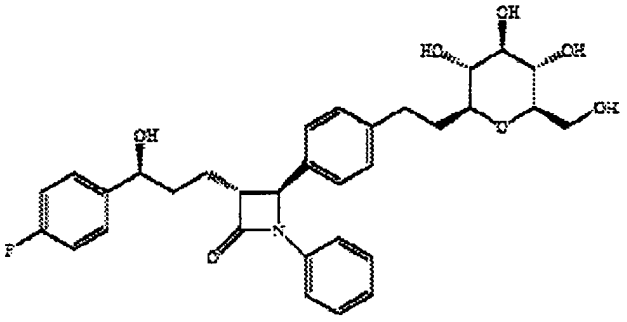
Pharmaceutical compositions comprising the compounds of Yumibe et al, and a lovastatin, pravastatin, fluvastatin, or simvastatin are specifically claimed [claims 17].

The pharmaceutical compositions can be administered in forms such as capsules, tablets, powders, etc., and can include excipients such as fillers, binders, buffers, etc. [column 17, lines 11-23]. The daily dose of the compound is about 0.001-30 mg/kg per day [column 17, lines 24-26]. The daily dose of the HMG reductase inhibitor administered in combination with the compound is 0.1-80 mg/kg per day in single or divided doses [column 17, lines 33-41]. The components may be administered separately [column 17, lines 49-512].

The difference in the beat-lactams taught by Yumibe et al. and the instantly claimed beta-lactams is that the instantly claimed lactams comprise C-glycosides and those of Yumibe et al. comprise O-glycosides.

Tomiyama et al teach beta-lactam compounds which are useful as serum cholesterol lowering agents [see abstract]. One preferred compound, compound 56 [page 18], shown below, is the same compound as that which is recited in instant claim 4:

56



Hypocholesterolemic beta-lactam-O-glucuronic acid conjugate derivatives are known, but the O-glycoside bonds in beta-lactam-O-glucuronate compounds can be hydrolyzed in the small intestine, possibly reducing the activity of the compounds [0003-0004]. Thus, hybrid beta-lactams having a C-glycoside, which is stable to metabolism by glycosidase and hydrolysis, were prepared [column 2, lines 3-10]. The compounds are excellent hypocholesterolemic agents and are expected to have reduced side effects compared to the O-glycoside compounds [0006].

Tomiyama et al. do not teach a combination of beta-lactam and HMG-CoA reductase inhibitor.

It would have been obvious to one of ordinary skill in the art to prepare a cholesterol-lowering composition comprised of a HMG-reductase inhibitor and a β-lactam taught by Tomiyama et al. The combination of beta-lactam cholesterol absorption inhibitor and HMG-reductase inhibitor is already known in the art, as taught by Yumibe et al. Tomiyama et al. teach modified beta-lactams comprising C-glycosides which are improved over Yumibe's O-glycosides, as discussed above. One of ordinary skill in the art could have substituted Tomiyama's modified beta-lactams for the beta-lactams in the combination taught by Yumibe et al. and would have predicted that the resulting composition would be effective for reducing plasma cholesterol levels and treating atherosclerosis.

Further, both cholesterol biosynthesis inhibitors and the β-lactams taught by Tomiyama et al. are known

in the art for reducing serum cholesterol levels. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Response to Arguments

Applicant argues that the combination of compound 56 of Tomiyama et al. and an HMG-CoA reductase inhibitor displays an unexpected synergistic effect. This effect is not unexpected, because it is known in the art that a combination of beta-lactam cholesterol absorption inhibitor and the HMG-CoA reductase inhibitor lovastatin results in a greater decrease in plasma cholesterol than either agent alone. See Davis (US 5,661,145, August 26, 1997), column 2, lines 11-13 and columns 7 and 8, Table 2. Further, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues that the combination of O-glycoside beta-lactam with HMG-CoA reductase inhibitor is not transferable to the corresponding C-glycoside beta-lactam because Tomiyama doesn't suggest it. This argument is not persuasive because Tomiyama's C-glycosides are an effective and more stable improvement over the O-glycosides taught by Yumibe. Thus the skilled artisan could conceive of using the C-glycosides in the same way as the O-glycosides were used, and would expect the compounds to be effective."

With regard to claim 33, Applicants respectfully submit that the foregoing cancellation of that claim renders the rejection thereof moot.

As for the rejection of claim 4, Applicants respectfully traverse the rejection thereof because a prima *facie case* of obviousness has not been established with respect to the claim as amended herein.

The Federal Circuit has ruled that a *prima facie* case of obviousness must establish: (1) some suggestion or motivation to modify the references; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Feb. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970). Applicants note that the "teaching-suggestion-motivation" test for obviousness is still applicable following the Supreme Court decision in KSR International Co. v. Teleflex Inc. 550 U.S. - , 82 USPQ2d 1385 (2007) and that there is no teaching, suggestion or motivation in the cited references to induce one of ordinary skill in the art to derive the present invention. A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

The examiner cites Yumibe, et al., U.S. 5,756,470 as teaching a combination of a cholesterol biosynthesis inhibitor, specifically HMG-CoA reductase inhibitors, and a beta-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis. The examiner further

cites Tomiyama, et al., U.S. 2004/0063929 as teaching the beta-lactam compound of the instant claim 4 as a useful serum cholesterol lowering agent which is stable to metabolism by glycosidase and hydrolysis.

However, the examiner acknowledges that Tomiyama, et al. do not teach the combination of the beta-lactam compound and a cholesterol biosynthesis inhibitor, much less the beta-lactam compound of claim 4 in combination with an HMG-CoA reductase inhibitor. Instead, the examiner contends that such a combination would be obvious to one of ordinary skill in the art.

The examiner further contends, in the response to Applicants' previous arguments, that the synergistic effect Applicants observe on the reduction of serum cholesterol by combining compound 56 of Tomiyama, et al., and an HMG-CoA reductase inhibitor would be expected in view of Davis, U.S. 5,661,145.

Claim 4 as presented herein presents a specific composition as a serum cholesterol lowering agent or preventive or therapeutic agent for atherosclerosis which comprises the combination of the C-glycoside beta-lactam compound 56 of Tomiyama, et al., and an HMG-CoA reductase inhibitor. This combination displays a significant pharmacologically synergistic effect with respect to the lowering of serum cholesterol that is not suggested by the use of either component individually, nor by the teaching of Yumibe, et al. Furthermore, this synergistic

effect of the combination of the recited beta-lactam compound and an HMG-CoA reductase inhibitor on serum cholesterol cannot be expected from the teaching of Davis which is directed to the reduction of plasma cholesterol. Indeed, Davis clearly states that "HMG-CoA reductase inhibitors alone do not lower plasma cholesterol levels in hamster and monkeys." (Col. 2, lines 18-20). In contrast, HMG-CoA reductase inhibitors do have an effect, albeit limited, on lowering serum cholesterol levels as shown in the data presented in Table 13 of the present invention.

However, prior to the present application, there was nothing to suggest that a combination of C-glycoside beta-lactams and HMG-CoA reductase inhibitors would have a synergistic effect with respect to serum cholesterol levels.

This synergistic effect of the combination of claim 4 herein is clearly shown by the data presented in Table 13 of the present application. In Table 13, the beta-lactam compound is the compound 56 of Tomiyama, et al., as recited in claim 4 and the HMG-CoA reductase inhibitor is atrovastatin.

As seen in Table 13, a combination prescription of compound 56 adminstered at 0.3 mg/kg/day with atrovastatin administered at 1 mg/kg/day lowered serum cholesterol in the test animals by 20.2%. In contrast, use of compound 56 alone at the same dosage lowered serum cholesterol by only 6.9% while atrovastatin alone at the same dosage lowered serum cholesterol by only 6.2%. Clearly when used together, the C-glycoside beta-lactam compound

56 and the HMG-CoA reductase inhibitor complement each other and produce a pharmacologically synergistic effect on the lowering of serum cholesterol. Such a synergistic effect between a C-glycoside beta-lactam compound and HMG-CoA reductase inhibitor on the lowering of serum cholesterol levels is not taught or suggested by Yumibe, et al., or Tomiyama, et al., or Davis.

Furthermore, the beta-lactam used in Davis is a compound of a specific chemical structure which does not conform to either the beta-lactam compounds having the -O-G group as disclosed in Yumibe, et al., the O-glycosides, or the beta-lactam compounds having the -C-G group as disclosed in Tomiyama, et al., and recited in Claim 4 of the present invention, the C-glycosides. Indeed, Davis fails to even mention O-glycoside or C-glycoside beta-lactams.

In view of the complex and multifaceted process of cholesterol absorption which takes place in the body and which is duly noted by Davis (Col. 1, lines 43-44), Applicants respectfully submit that a teaching of reduction of plasma cholesterol by a combination of an HMG-CoA reductase inhibitor and one series of beta-lactam compounds, would not lead one to expect a similar effect on serum cholesterol by the combination of an HMG-CoA reductase inhibitor and a completely different series of beta-lactam compounds.

Furthermore, the examiner's reliance on Yumibe, et al., as teaching the combination of an O-glycoside beta-lactam and an

HMG-CoA reductase inhibitor to show that it would be obvious to substitute the C-glycoside beta-lactam of Tomiyama, et al., is, respectfully, misplaced.

Although Yumibe, et al., discloses the use of an HMG-CoA reductase inhibitor with a beta-lactam compound, as has previously been pointed out, like Davis, the beta-lactam of Yumibe, et al., is also a different class of compound, i.e., an O-glycoside beta-lactam, having a different mode of activity than the beta-lactam of the present invention, which is a C-glycoside beta-lactam. There is no teaching in Yumibe, et al., to suggest a synergistic activity between the O-glycoside beta-lactam of the reference and the HMG-CoA reductase inhibitor much less between the C-glycoside beta-lactam of Tomiyama, et al., and an HMG-CoA reductase inhibitor as recited in claim 4 of the present invention.

The only discussion in Yumibe, et al., of synergistic effect relating to the use of an HMG-CoA reductase inhibitor is the brief mention at column 2, lines 11-20 that "Combination therapy of an HMG-CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patient than either agent in monotherapy". However, neither the O-glycoside beta-lactam of Yumibe, et al., nor the C-glycoside beta-lactam of Tomiyama, et al., or the present invention are considered to be bile acid sequestrants, the beta-lactams and the bile acid sequestrants have completely different mechanisms of

operation. Accordingly, the teaching of Yumibe, et al., relating to a synergistic effect of HMG-CoA reductase inhibitors and bile acid sequestrants is not relevant to the combination of the C-glycoside beta-lactam of compound 56 and an HMG-CoA reductase inhibitor.

Furthermore, the fact that Yumibe, et al., teaches the combination of an O-glycoside beta-lactam with an HMG-CoA reductase inhibitor is not transferable to the Tomiyama, et al., teaching of the C-glycoside beta-lactam compound as there is nothing in Tomiyama, et al., to suggest a combination of that beta-lactam with another cholesterol inhibiting compound, nor that any appreciable synergistic effect would be expected.

As further evidence of the unexpected pharmacological effect obtained by the combination of the C-glycoside beta-lactam compound 56 and an HMG-CoA reductase inhibitor over similar combinations of C-glycoside beta-lactams and HMG-CoA reductase inhibitors or the respective beta-lactams and HMG-CoA reductase inhibitors alone, Applicants present the herewith filed Declaration of Kazuhiro Kosakai, showing the effect of such compounds and combinations on levels of serum LDL and HDL cholesterol.

As is readily evident from the results provided in Tables 1 and 2 of the declaration, the effect of the combination of compound 56, the C-glycoside beta-lactam recited in Claim 4 of the present invention, and HMG-CoA reductase inhibitors is

significantly greater than that observed with compound 56. In addition, when compared with corresponding combinations of an O-glycoside beta-lactam, compound A in the experiments of the Declaration, and the same HMG-CoA reductase inhibitors, Applicants' combination of compound 56 and HMG-CoA reductase inhibitors exhibits a greater synergistic effect.

Thus, even if Yumibe, et al., did teach a synergistic effect between O-glycoside beta-lactams and HMG-CoA reductase inhibitors, which the reference clearly does not do, the significant improvement in such effect obtained using the C-glycoside beta-lactam compound of Tomiyama, et al., would not be obvious as there is nothing to teach substitution of a C-glycoside beta-lactam for the O-glycoside beta-lactam of Yumibe, et al.

Furthermore, even if one did make the substitution, for which there is no suggestion in the prior art, one would only expect the same level of synergistic effect obtained using the O-glycoside beta-lactam, not the enhanced effect evidenced by Applicants' combination of the C-glycoside beta-lactam compound 56 and HMG-CoA reductase inhibitors.

In view of the foregoing, Applicants respectfully submit that it would not be obvious to one of ordinary skill in the art, knowing the action of the compounds of Yumibe et al. to expect the improvements exhibited by combining the cholesterol biosynthesis inhibitors of Yumibe et al. with the C-glycoside

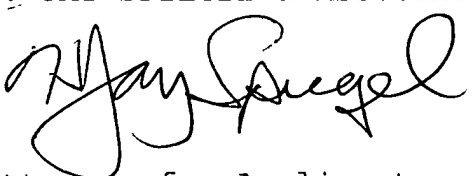
beta-lactams of Tomiyama et al. Furthermore, there is nothing to suggest that a substitution of C-glycoside beta-lactams for the different series of beta-lactams in Davis would result in a similar improvement in the effect on cholesterol reduction. Because the actions of the beta-lactams of the respective references are different, Applicants respectfully submit that there is nothing in either reference to support the combination thereof as urged by the examiner and that a *prima facie* case of obviousness has not been established.

Accordingly, Applicants respectfully submit that the present rejection under 35 U.S.C. 103(a) is without support and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that the claims as amended herein are allowable over the prior art and a notice of allowance is respectfully requested.

Respectfully submitted,

H. JAY SPIEGEL & ASSOCIATES



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